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TITLE: Silver Foam Technologies Healing Research Program

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CONTRACTING ORGANIZATION: Noble Biomaterials

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Silver Foam Hemostatic Bandage as an Effective Hemostatic and Antimicrobial Agent in the Treatment of Traumatic Wounds Requiring Secondary/Delayed Primary Closure

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13. SUPPLEMENTARY NOTES

14. ABSTRACT The purpose of this research is the development of a hemostatic antimicrobial hydrophilic foam bandage capable of reducing the bacterial bioburden, blood product requirements and facilitate the definitive surgical intervention to close the wound. Successful accomplishments to date have been the development of a medical grade hydrophilic foam capable of absorbing fifteen time its weight in fluid and having hemostatic properties allowing for the absorption and coagulation of heparinized human blood. The antimicrobial and biocompatibility tests are presently being evaluated and it is anticipated that clinical testing will begin in January of 2009.

15. SUBJECT TERMS
None provided.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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Table of Contents

1. Introduction:

   Hemorrhage and infection continue to attribute to the morbidity and mortality of traumatic wounds. The mechanism of injury of these wounds prevents the use of primary closure as a treatment option. Delayed primary closure or closure by secondary intent are clinical options but require the need of a dressing or bandage. The goal of this research is to develop antimicrobial hemostatic hydrophilic foam bandage that could be employed when primary closure is not an option. The bandage design would be such that it could be left in place until a definitive surgical procedure could be performed while at the same time facilitate hemostasis and reducing bacterial bioburden

2. Body:

   Task 1: Research open-end hydrophilic foam:

   The concept of an open-end hydrophilic foam bandage was based on the fact that the open-end would allow migration from all exposed surfaces of the foam which would facilitate both the transport of fluids and the migration of cellular elements. Essential to the foam construct was that it was non toxic, had been used in prior medical applications, was capable of absorbing and retaining sufficient fluid into its construct, allowed and demonstrated the uniform distribution of a hemostatic agent, allowed for the uniform distribution of a metallic antimicrobial metal, and could be sterilized without disruption of any of these attributes.

   The application of silver to the foam can be achieved by employing a number of processes that are the intellectual property of Noble Biomaterials. Based on this knowledge prototype drawings were made incorporating these different concepts into bandage design. These prototypes were then researched to assess their uniqueness and appropriateness as it related to the scope of this grant. The prototypes listed in Appendix A were selected as appropriate and

unique to this study. Review of the existing medical foam products also revealed that an antimicrobial hemostatic hydrophilic bandage was presently not available. The uniqueness of this concept was likewise supported by an independent patent search and subsequent patent application. Appendix B.

Previous research with Dicon foam manufactures had produced hydrophilic foam which had chopped silver coated nylon fibers incorporated into the foam. The foam has proven to be antimicrobial for a variety of organisms. The antimicrobial effect was based on a weight ratio of ten percent silver nylon fiber or X-static fiber. This then became the base line for the percentage of silver required to be incorporated into the bandage for antimicrobial effect.

Research in collaboration with Lendell foam manufactures produced a medical grade foam which proven efficacy in medical application. The foam was non toxic and had an absorption ratio of fifteen grams of fluid to every gram of foam. This was based on a two minute adsorption period followed by a thirty second drip period. This period of time was then selected as the base line for adsorption of heparinized blood for the hydrophilic foam.

Documentation of uniform distribution of both hemostatic and antimicrobial agents was essential for an open-end hydrophilic foam bandage. To determine this metalized silver glass beads were incorporated into the foam extrusion process and evaluated microscopically for uniform distribution. Microscopic examination Appendix C shows the distribution of the silver metal throughout the foam.

It is anticipated that the final prototype will be completed by the end of December 2008. It will be open-end hydrophilic foam capable of being manufactured in two thicknesses one quarter inch and three quarter inch. The manufacturing process will allow a foam product

that can be cut to standard bandage sizes contain between five to ten percent silver, have a absorption capacity of fifteen to one, and will have proven antimicrobial efficacy and biocompatibility testing.

Task 2: Metalized open-end hydrophilic foam

The uniform distribution of silver throughout the foam is required in the use of any open foam product. Noble Biomaterials has developed the process for the metallization of hydrophobic foams for use in negative therapy dressings. The process allows for the uniform distribution of silver and the constant sustained release of silver over an extended period of time. This same process forms the basis for the metallization of the hydrophilic foam. Though the hydrophobic foam repels fluid and the hydrophilic foam absorbs fluids the metallization process provided equal and uniform distribution. What was critical was the number of pores per square inch. Pore size greater than fifty pores per square inch prevented the uniform metallization of the hydrophilic foam.

Task 3: Identify and incorporate topical hemostatic agents:

There are many topical agents that are employed to activate the hemostatic cascade. Though many agents are employed in a variety of clinical settings their ability to be incorporated into hydrophilic foam was unknown. Certain organic agents were eliminated based on previous degradation in the manufacturing process[1,2] or because of the risk of viral transmission. It was elected to use those agents known to be effective in determining the activated clotting time developed by time developed by Dr. Paul Hattersley.[3] Initial testing showed the agents capable of being incorporated but not of sufficient concentration to achieve hemostasis.[4]

Using the ratios set established for the activated clotting time and the absorption ratio for the hydrophilic foam increasing concentrations of

the hemostatic agents where added to the foaming process to account for the unknown antimicrobial effect of the silver glass beads. This resulted in only two topical agents, Zeolite and Silver Glass, being able to be incorporated into foam without congealing. Appendix D.

Testing of both the Zeolite and Silver Glass foams was undertaken to evaluate their ability to absorb and facilitate coagulation of heparinized human blood samples. Two inch by two inch three quarter inch samples where subjected to ten milliliters of heparinized blood. Findings revealed that increasing concentration of silver glass resulted in a tighter foam pore size with increasing ability to absorb blood. The increasing concentration of silver also allowed the blood to be absorbed using less of the sponge material. The Zeolite showed just the opposite findings with larger pore size, residual blood being present with no residual sponge being present Appendix D.

Task 4: Establishing the antimicrobial activity of the hydrophilic foam:

The antimicrobial activity of the silver glass hydrophilic foam is unknown at this time and is being tested by an independent laboratory. Previous evaluation and testing of Noble Biomaterials products have shown effective eradication of numerous organisms over a seventy two hour period.[5] It is anticipated that similar results will be present and is presently under evaluation.

Task 5: Determine the safety profile of silver hydrophilic foam:

The hydrophilic foam, hemostatic agents and metallization process have had previous regulatory approval and have been employed in clinical settings. Biocompatibility of the silver glass hydrophilic foam is presently being evaluated by an independent lab. Sterilization of the product is scheduled and both antimicrobial and biocompatibility will be done to assure the efficacy of the product has not been altered by the sterilization process.

Task 6: Assess the logistic cost of using the silver foam bandage in clinical setting:

On August 09, 2008 authorization and funding was granted to undertake the clinical testing of silver foam bandage. Contacts have been established with Dr. Peter Berger of the Geisinger Health System and Dr. Evan Renz of the Brook Army Burn Center as to the feasibility for clinical evaluation. Submission of the clinical protocol, informed consent, tracking forms and CITI training have been sent to Dr Jeffrey Stephenson for regulatory approval.

3. Key Research Accomplishments:
   - Ascertain that an antimicrobial hemostatic hydrophilic foam bandage was not present in the existing inventory.
   - Incorporate existing topical hemostatic agents into hydrophilic foam.
   - Produce a variety of hemostatic hydrophilic foam prototypes.
   - Design and produce a hydrophilic hemostatic foam dressing that could be tested using standard activated bleeding time.
   - Produce a hemostatic hydrophilic foam bandage capable of absorbing and clotting heparinized human blood.

4. Reportable Outcomes:
   a. Provisional Patent Application Serial No. 60/894,777
   b. Presentation at Product Line Review Biomaterials and Nanomedicine for Telemedicine and Advanced Technology Research Center 5 August 2008
   c. Extended award for clinical evaluation for Silver foam Technologies Healing Research Program 9 August 2008

5. Conclusions:

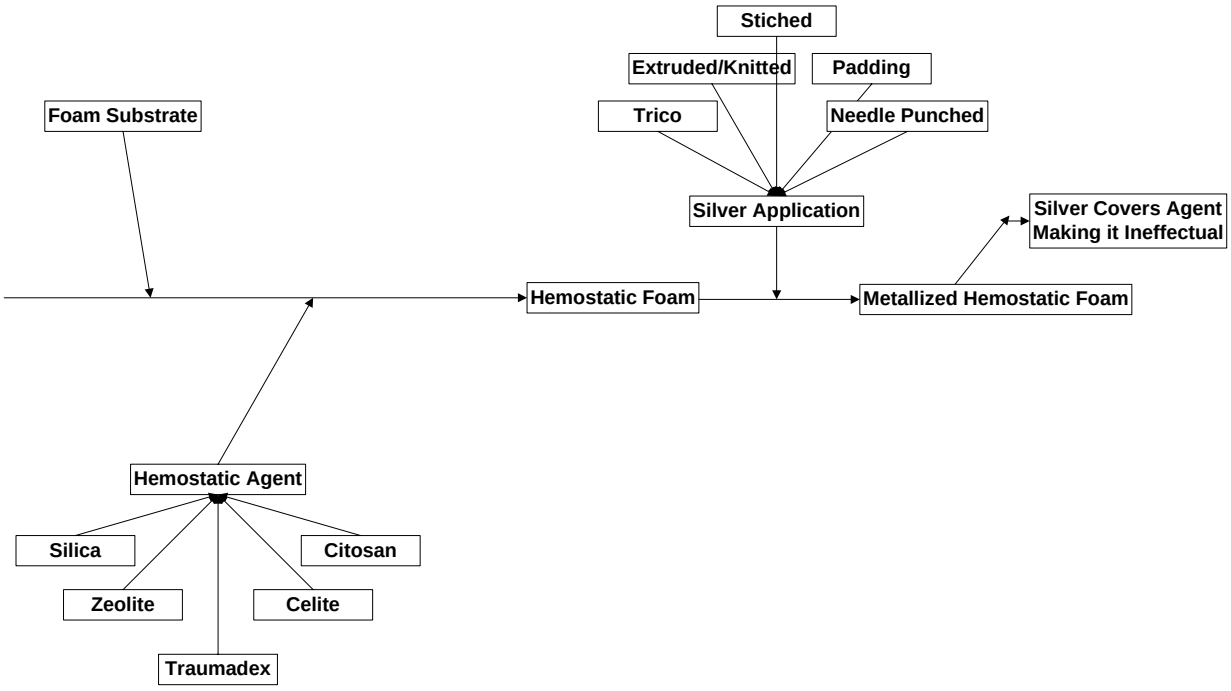
The completed research to date has established that a multifunctional interactive hemostatic hydrophilic foam bandage is capable of being produced using existing medical products and technologies. It is anticipated that effective antimicrobial efficacy will also be present based on prior research. The final bandage will have the ability to absorb exudate more efficiently allowing for fewer dressing changes, reduce bacterial bioburden thereby decreasing the incident of secondary surgical infection, have hemostatic properties to activate the hemostatic cascade leading to diminished use of blood products.

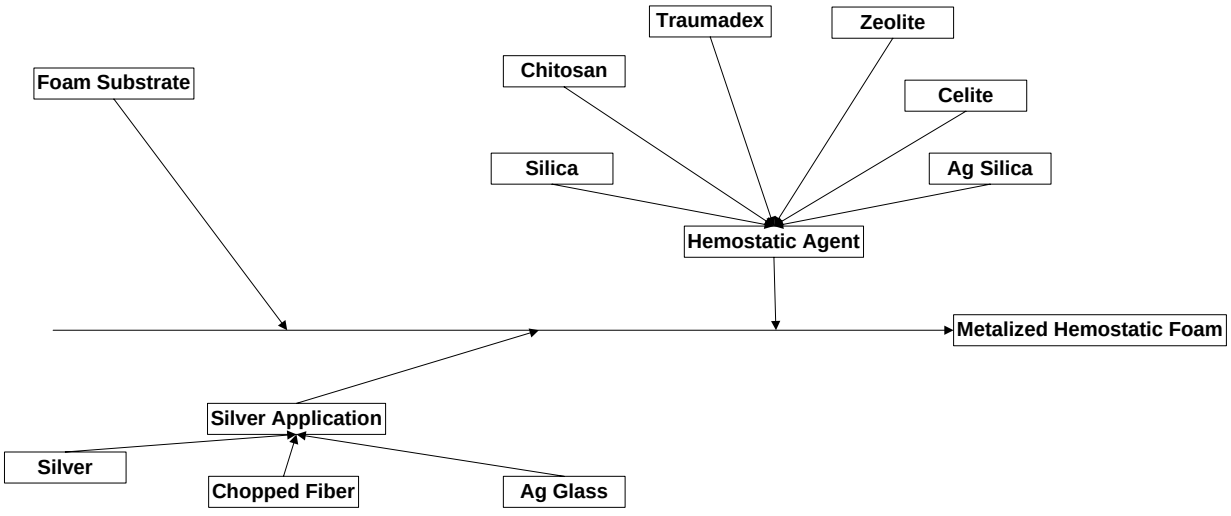
6. References:

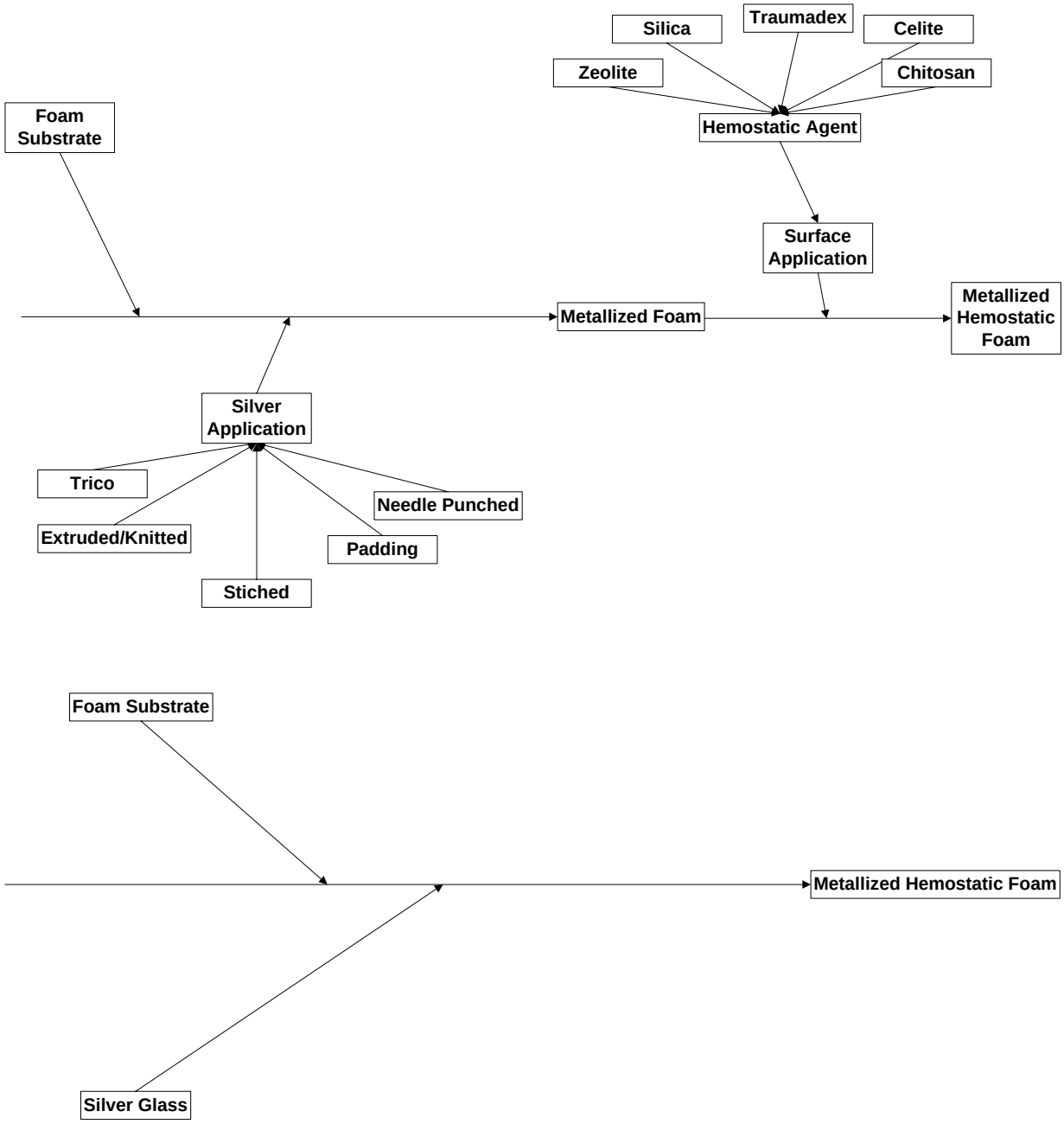
1. Travis, J. *Building Better Bandages*, 1999, ScienceNewsOnline; 155; 25.
2. Heiskell, L. Tang, D. *Advances in Hemostatic Bandages*; 2003,http://www.navyjncc.com.
3. Hattersley, PG *Activated coagulation time of whole blood.* JAMA 1966 May 2; 1965(5): 436-440
4. Moore M *Silver Foam Technologies Healing Research Program 5 August 2008 Product Review* Frederick, Maryland.
5. Mac Keen, P Silver-Coated Nylon Fiber as an Antibacterial Agent 1987 Antimicrobial Agents and Chemotherapy Jan 87; 91-99.

8. Appendices:

A.



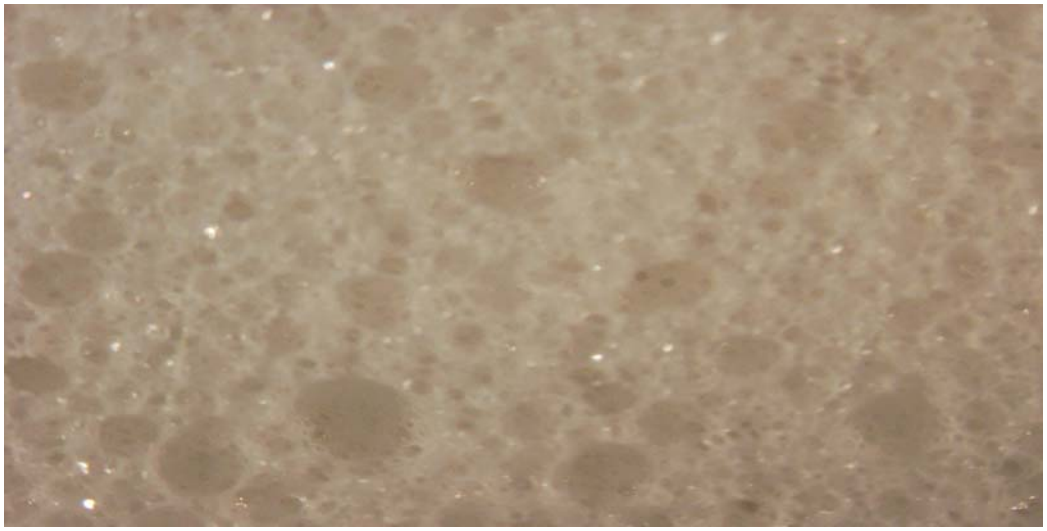




B. Provisional Patent Application Serial No. 60/894,777

	Amount	Outcome	Pore Size	Comments
Ag Glass	18 gms	Foam	OK	

C.



D.

Results at Lendell 8-29-2008

Celite 501	18 gms	Foam	OK	
Traumadex	12 gms	Foam	OK	
Zeolite	18 gms	Foam	OK	
Chitosan	18 gms	Failed	NA	Congealed when mixed
Silica Gel	18 gms	Foam	Large	May be able to alter with process
Ag Glass	36 gms	Foam	OK	Smaller poor size than 18 gms
Zeolite	36 gms	Foam	OK	Larger pore size than 18 gms
Silica Gel	36 gms	Failed	NA	Congealed when mixed
Celite	36 gms	Failed	NA	Congealed
Ag Glass	54 gms	Foam	OK	Smaller pore size than 36 gms
Zeolite	54 gms	Foam	OK	Larger pore size than 36 gms

Notes:
Absorption time is based on two minute in fluid and thirty seconds drip. Basis for dry verses wet weight
6.42 Gms -> 96.83 Gms ∆ 14.96

Based on 1500 ml absorption at 12 mgm per ml

Coagulation Trials Zeolite 9-13-2008

Zeolite Chopped	1 min	2 min	3 min	4 min
18 gms Zeolite 10 ml blood	Absorbed No residual	Absorbed No residual	Absorbed No residual	Absorbed No residual
36 gms Zeolite 10 ml blood	Absorbed No residual	Absorbed No residual	Absorbed No residual	Absorbed No residual
54 gms blood 10 ml blood	Absorbed No residual	Absorbed No residual	Absorbed No residual	Absorbed No residual

Coagulation Trials Zeolite 9-13-2008

Zeolite Sponge 2x2x3/4	1 min	2min	3min	4min
18 gms Zeolite 10 ml blood	10 ml blood absorbed Blood on compression	10 ml blood absorbed Blood on compression	10 ml blood absorbed Blood on compression	10 ml blood absorbed Blood on compression
36 gms Zeolite	10 ml blood	10 ml blood	10 ml blood	10 ml blood

10 ml blood	absorbed Blood on compression	absorbed Blood on compression	absorbed Blood on compression	absorbed Blood on compression
54 gms Zeolite 10 ml blood	3 ml blood not absorbed Blood on compression	3 ml blood not absorbed Blood on compression	3 ml blood not absorbed Blood on compression	3 ml blood not absorbed Blood on compression

Coagulation Trials Silver Glass 9-13-2008

Silver Glass Chopped	45 sec	1 min	2 min	3 min
18 gms Silver Glass 5 ml blood	Complete absorption Residual sponge present	Same	Same	Same
18 gms of Silver Glass 10 ml blood	Complete absorption No residual sponge available	Same	Same	Same
36 gms of Silver Glass 10 ml blood	Complete absorption Residual sponge present	Same	Same	Same
54 gms of Silver Glass 10 ml blood	Complete absorption Greater amount of residual sponge present	Same	Same	Same

Coagulation Trials Silver Glass 9-13-2008

Ag Glass Sponge 2x2x3/4	1 min	2 min	3 min	4min
18 gms Silver Glass 5 ml of blood	5 ml absorbed sponge areas for more absorption Blood on compression	5 ml absorbed sponge areas for more absorption Blood on compression	5 ml absorbed sponge areas for more absorption No blood on compression	
18 gms of Silver Glass 10 ml of blood	10 ml absorbed with no open areas Blood on compression	10 ml absorbed with no open areas Blood on compression	10 ml absorbed with no open areas No blood on compression	
36 gms of Silver Glass 10 ml of blood	10 ml of blood absorbed with areas for more absorption No blood on compression			
54 gms of Silver Glass 10 ml of blood	10 ml of blood absorbed within 30 sec with more areas for absorption than seen in 36 Gm sample No blood on compression			